
OFFICE OF NEW ANIMAL DRUG EVALUATION REVIEWER'S CHAPTER

REQUESTING A BIORESEARCH MONITORING (BIMO) INSPECTION

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I. PURPOSE

This document describes:

- the Bioresearch Monitoring (BIMO) program
- Office of New Animal Drug Evaluation's (ONADE) criteria for initiating a BIMO request
- how ONADE reviewers will request a BIMO inspection
- the Office of Surveillance and Compliance's (OSC) Premarket Compliance and Administrative Actions Team (HFV-234, formerly the BIMO Team) responsibilities when they receive a BIMO request

II. WHAT IS BIMO?

BIMO programs are used to inspect Good Laboratory Practices (GLP) study facilities, clinical investigators (CI), or sponsors/ contract research organizations (CRO)/monitors. The BIMO compliance programs help to assure the integrity of scientific testing and the reliability of test data submitted to FDA. BIMO inspections (audit procedures or real-time) allow the agency to assess whether safety and effectiveness or bioequivalence data of regulated drug products submitted to FDA are acceptable. This assessment includes a determination if adequate data integrity measures are in place for electronic data collection (EDC) systems. At CVM, the BIMO programs are overseen by the Office of Surveillance and Compliance's (OSC) Premarket Compliance and Administrative Actions Team (HFV-234, formerly known as the BIMO Team).

CVM monitors the conduct of pre-approval studies with three compliance programs:

1. Clinical Investigators [CP 7348.811]

These inspections will look at an investigator conducting a study under Good Clinical Practice (GCP) Guidelines, typically an effectiveness study (including laboratory effectiveness studies), or a particular clinical investigator for a multi-site effectiveness study.

2. Good Laboratory Practice Compliance Program (CP) [CP 7348.808]

Inspections under this program will look at studies and facilities conducting studies under Good Laboratory Practices (GLPs) 21 CFR Part 58.

It is important to understand that a GLP facility is not necessarily or always by default considered a CRO. See below for more information on the legal definition of CRO.

3. Sponsors, Contract Research Organizations (CRO), and Monitors¹
[CP 7348.810]

These inspections are intended to evaluate the sponsor's responsibilities under 21 CFR 511.1 and 514. As examples, ONADE may request this type of inspection as 1) a follow-up to a clinical investigator inspection(s) that had questionable results of a systematic nature (e.g., perceived inadequate monitoring), 2) if there are numerous clinical investigators with small case numbers, 3) if the source data have been moved from clinical investigator to sponsor, or 4) for a foreign study.

It is important to understand that CRO means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration (21 CFR 511.3). Most clinical investigators and GLP laboratories do not fit this definition, because being a clinical investigator or laboratory is not an obligation required in the regulation. Ergo, just conducting a study on behalf of the sponsor does not make the laboratory doing so a CRO. They must be carrying out an obligation that is required under the regulations (e.g., monitoring investigations). If there is any doubt, contact the Team Leader of the Premarket Compliance and Administrative Actions Team (HFV-234).

There are three categories of inspections in the BIMO program.

1. Directed inspections: These are the most common type of inspections requested by ONADE reviewers. There are two types of Directed inspections: real-time and data audit inspections.
2. For Cause inspections: These inspections are carried out in response to specific information that raise concerns of possible fraudulent activities or complaints. For Cause inspections can be requested both by ONADE review divisions and HFV-234.
3. Surveillance inspections: These inspections are typically done for GLP facilities and Sponsor/CRO/Monitor. Surveillance inspections are typically requested by HFV-234 in consultation with reviewers within CVM.

¹ This is the title of the Compliance Program. Note that monitoring is a responsibility of the sponsor and if someone other than sponsor carries this responsibility they are considered a CRO.

III. CONSIDERATIONS BEFORE REQUESTING A BIMO INSPECTION

A. Who is responsible for initiating a BIMO request?

ONADE initiates the BIMO inspection process for Directed inspections and in certain cases for For Cause inspections. Scientific reviewers or members of the Quality Assurance Team (HFV-184) in ONADE determine the need for an inspection of safety, effectiveness or bioequivalence studies.

B. When in the review process should a BIMO inspection request be initiated?

A BIMO inspection can be requested at any time before or after approval of a new animal drug. Typically, ONADE initiates BIMO inspections during the phased review process (See Guidance for Industry #132 Administrative Applications and the Phased Review Process) of a generic investigational new animal drug (JINAD) file or investigational new animal drug file (INAD).

Typically, there are two times ONADE requests a BIMO inspection.

1. During the conduct of the study (real-time [also known as in-life inspection]), and
2. After the study has been completed (data audit).

A real-time inspection allows us to observe certain aspects of the study as they are being conducted or to look for particular issues of concern to the reviewer. A data audit inspection allows for a full accounting of the study, and may be conducted before or after the data are submitted to CVM. Either type of inspection is acceptable based on the information needs of the reviewer.

ONADE should request an inspection as early as possible to allow sufficient time to schedule the inspection, especially if it will be an inspection outside the United States (a.k.a., foreign inspection). ONADE reviewers can use the information provided in a notice of claimed investigational exemption (NCIE, is also called a "drug shipment notice") to plan the BIMO inspections (see P&P 1243.4066 for more information on NCIE). Alternatively, ONADE can request a BIMO inspection when we receive the study data for review if the start of the study is unknown or there is more benefit to inspecting a study after it is completed.

C. Which entities (study/test facility/clinical investigator/sponsor/CRO/monitor) should be nominated for a BIMO inspection?

The ONADE review group determines which studies are pivotal to making scientific decisions for a specific new animal drug application. All pivotal studies are potential candidates for a BIMO inspection. If a study is conducted at multiple sites, the entire study, may be subject to a BIMO inspection. However, more commonly, one or more sites are chosen for inspection from multiple sites. The ONADE Quality Assurance Team (HFV-184) may also determine that a study or facility requires a BIMO inspection. Before the Quality Assurance Team requests a

BIMO, they should discuss this with any involved review divisions in ONADE to ensure BIMO requests are a coordinated effort.

When deciding whether an inspection is needed, it is helpful to determine the presence of a BIMO inspection history of the entity in the Center's Corporate Database Portal (CDP) BIMO module (BIMO Assignment Listing/EIR Tracking).

Consider the following when deciding whether to request a BIMO inspection:

1. Is the study considered pivotal? A "pivotal" study ONADE considers by us to be an essential part of the basis for the approval of a new animal drug.
2. Is the entity "new" (i.e., has no BIMO inspection history)?
3. If the entity has been inspected before, has it been some time (usually two to three years) since the entity has been inspected?
4. If the entity has been inspected before, was the outcome classified as "voluntary action indicated" (VAI) or "official action indicated" (OAI)?
5. What were the previous problems, if any, with the entity?
6. Is the product a new chemical substance/compound (or is it a new delivery system)? Is there some other unique circumstance that is a concern?
7. Were there issues about the validity of the data that were raised during review of the study (e.g., substantial errors in the report, unable to reconcile summary data with the raw data, unexplained data errors, omission of critical data, etc.)?

In addition to the above examples, there may be other situations where BIMO inspection may be necessary.

IV. HOW TO REQUEST A BIMO INSPECTION

A. Requesting a BIMO Inspection

In ONADE, inspection requests for BIMO inspections are initiated at the team level and processed through the team leader or division director, then sent to and processed by the Center's HFV-234 in OSC, and finally sent to the district office investigational branches or to the Office of Regulatory Affairs (ORA) international operations group for studies in other countries.

The team leader, division director, or a designated appointee, prioritizes the inspection requests within their review group (if necessary). Each review group determines if the receipt of a data submission, an NCIE or other review circumstances will result in inspection of the investigator(s). The review group also determines if the presence of a CVM reviewer is necessary during the inspection. If a CVM reviewer will be present on the inspection, that reviewer must have FDA credentials. There is a Credential Request Form (2115 Form) that must

be used to get credentials.² See the CVM Standard Operating Procedure entitled "Obtaining or Renewing FDA Official Credentials".³

Once the ONADE reviewer has discussed the proposed inspection with their division management and it is determined that a BIMO inspection is necessary and whether the presence of an ONADE reviewer is necessary during the inspection, submit the BIMO inspection request form to HFV-234 using the following procedures.⁴

1. Step 1

Complete a Bioresearch Monitoring Inspection Request form for the type of inspection being requested. There are two separate forms for inspection requests: a) GLP and clinical investigators form and b) sponsor and CRO form. Use the GLP and clinical investigator form for inspections you want to have conducted for GLP compliance and clinical investigator studies. Use the sponsor and CRO form for inspections you want conducted on sponsor or CRO conducted studies. Follow the instructions within the forms to guide you on what information to provide regarding the inspection request.

In the request, provide information that will help the field consumer safety officers (CSOs) focus on the areas of the study you are interested in inspecting. For example, provide the individual animal data for those sections of the study you want inspected, if applicable.

2. Step 2

Because at this time the field does not have access to our database (i.e., CDMS), include copies of any appropriate documentation (e.g., study protocol, NCIE, final study report, data listing [e.g., SAS printouts], etc.) if available. If a CVM employee will be accompanying the field CSO on a BIMO inspection, include a completed "Inspection Participant Form" with the BIMO request.⁵ All documentation provided in support of the BIMO request should be in electronic form.

3. Step 3

Save the BIMO Inspection Request form and supporting information in a folder with the last name of the reviewer and the INAD number and, if

² The link to the FDA Forms Page on Inside.FDA is at:

Internal information redacted. Use search to find the Credential Request Form (2115).

³ The SOP lives in SharePoint in the CVM Environmental Health and Safety Security SharePoint site.

Internal information redacted.

⁴ The BIMO Request Forms are found on the ONADE Forms SharePoint page.115

⁵ The inspection participant form can be found on Inside.FDA on the BIMO Documents, Templates & Associated Process Maps page. Form number 000452 at:
Internal information redacted.

necessary, site location on the shared drive Internal information redacted.. Send an email to the CVM BIMO Requests Mailbox to inform HFV-234 about the request, include a statement in the email that indicates supervisory (team leader and/or division director) concurrence (if necessary per your divisions' policy), and include them in the cc: line of the email. Include a direct link to the location of your folder in the Internal information redacted. folder in the email.

Note that BIMO inspection requests are not routed through the Document Control Unit (DCU).

4. Step 4

Contact HFV-234 using Internal information redacted. if you need to update your request based on new information you find as you review the data. HFV-234 forwards the supporting materials to the district office for the field CSO to use during the inspection visit. ONADE communication with HFV-234 and the field CSO is important throughout the inspectional process. ONADE should inform HFV-234 of inspection dates and scheduling or if there is a date change or extension.

B. OSC's HFV-234's Responsibilities

When a request for BIMO inspection is received, HFV-234 will, within two weeks of receiving the request, do the following:

1. Step 1

Assures that all the necessary information relevant to the inspection request is provided.

2. Step 2

Accesses appropriate databases to assess inspectional history.

3. Step 3

Concurs or discusses any duplicative requests with the review division.

4. Step 4

Assigns a control number if an inspection is assigned or determines if an inspection will not be assigned, and informs the review division on the status of the inspection request.

5. Step 5

Within the established timeframe of two weeks, HFV-234 issues the inspection request to the appropriate field office, or ORA, if it is a foreign inspection.

6. Step 6

Maintains communication with ONADE reviewer and the field CSO throughout the inspectional process, as appropriate.

7. Step 7

Maintains records (e.g., emails and other documentation) and the Center's BIMO database and provides Establishment Inspection Reports (EIR) information when available to assist review groups in ONADE. Note: HFV-234 updates the BIMO database and posts EIR information within a week of being received from ORA.

8. Step 8

Files a copy of all BIMO documents in the appropriate administrative record [e.g., (J)INAD/(A)NADA] after the BIMO inspection and any associated reviews that have been completed.

Note: If you are looking for specific information, contact HFV-234 to inquire on the status.

V. REFERENCES

Code of Federal Regulations (Title 21)

Part 58 – Good Laboratory Practice for Nonclinical Studies

Part 511.1, 511.3 and 514 – New Animal Drugs for Investigational Use

Guidance for Industry

#132 Administrative Applications and the Phased Review Process

CVM Program Policies and Procedures Manual

1243.4066 - Notice of Claimed Investigational Exemption (NCIE)

FDA Compliance Program Guidance (CPG) Manual

CP 7348.808 – Good Laboratory Practice

CP 7348.810 – Sponsor, Contract Research Organizations, and Monitors

CP 7348.811 – Clinical Investigators

CVM Standard Operating Procedure

Obtaining or Renewing FDA Official Credentials

VI. VERSION HISTORY

November 16, 2001 – Original version

March 1, 2010 – The 1243.8220 document was reviewed by ONADE and Office of Surveillance and Compliance BIMO Team to determine if any changes needed to be made. The status check information was moved to a separate P&P. Edits were made to include more specific information, information for generic animal drug applications and investigational files, and reformat the document and make it conform to ONADE document principles.

November 14, 2014 – The 1243.8215 document was reviewed by ONADE and Office of Surveillance and Compliance BIMO Team to determine if any changes needed to be made. Edits were made to update the inspection request procedure, include information about categories of inspections, and made the document relevant for sponsor/monitor inspections.

April 25, 2018 – Revisions made to update the process to include timeframes for HFV-234, links to BIMO resources. Internal information was redacted from the FDA.gov version of this document.

August 6, 2018 – Revised to include a reference to the need for FDA credentials if a CVM reviewer is participating in an inspection to section IV. A.

December 18, 2018 – Revised to correct a typographical error.

March 1, 2019 - Changed the document to no longer link directly to FDA Forms. Link in footnote 2 now goes to the FDA Forms Page on Inside.FDA and reader is instructed to search for the Credential Request Form (Form 2115). Link in footnote 4 now goes to the BIMO Documents, Templates and Associated Process Maps page on Inside.FDA and reader is instructed to search for the Inspection Participant Form (Form 000452).

May 8, 2019 – Updated to include reference and link to the standard operating procedure for getting or renewing FDA credentials.